REMARKS

Claims 33-36 are pending. The Applicants note an error on the Office Action Summary sheet, which states under 4a) that "claims 24-31 are withdrawn from consideration"; Applicants believe this should recite claims 27-31. However, as the current amendment also cancels claim 24, and replaced new claim 33 for claim 24, the Applicants have cancelled claims 24-31 accordingly.

Rejection - 35 USC §112, second paragraph

Claims 24 and 32 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. It is assumed that Claim 32 is rejected for being based upon Claim 24.

Sections A, B and C of the Official Action are believed addressed by the new claim 33, due to the recitation of a) "inputting the coordinates of a target protein", which clearly includes the side chains; b) the "testing" and "selecting" language; and c) the "coordinates" language. Applicant submits the rejection should be withdrawn.

D. The Examiner has objected to step c) as being unclear. Without admitting the propriety of the rejection, and in the interests of furthering the prosecution, the Applicant has changed new claim 33 to recite a "decrease" in immunogenicity of a variant protein instead of an "altered" immunogenicity. Applicant believes this obviates the rejection, as only those alterations leading to decreased T cell immunogenicity are recited.

The Applicant does wish to point out, however, that contrary to the Examiner's position, not every change in an amino acid sequence will alter immunogenicity.

E. The Examiner has objected to the language of step b) of Claim 24 with respect to the expression "removes...by creating." Applicant believes new claim 33 obviates the rejection as this language has been removed.

F. The Examiner states that Claim 24 is indefinite for failing to recite a final process step that agrees with the preamble of the claim. Applicant believes new claim 33 obviates the rejection, as the preamble is to "screening for altered variant target proteins with decreased immunogenicity", and the steps of "testing" and "selecting".

G. The Examiner has rejected Claim 24 for being unclear about whether step b.ii is related to step a). Applicant believes new claim 33 obviates the rejection, as the "applying" step is now done on the target structure.

H. The Examiner states that Claim 24, step b) in allowing substeps to be applied in any order is ambiguous and unclear.

Applicant respectfully submit that the substeps can be applied in any order, however, Applicant submits this is not ambiguous, particularly in light of new claim 33. In one case, the computational design program is done first, creating variants potentially both within a T cell epitope or outside it, and then the immunogenicity filter follows, creating at least one (or an additional) variant T cell epitopes and potentially other variant positions. The variant(s) are synthesized, tested and selected. Applicant submits this is not ambiguous. Alternatively, the immunogenicity filter is done first, creating one or more variant T cell epitopes, and then the computation design program is done on the protein. If the computation design program "changes" the variant T cell epitope "back" to the wild-type, then presumably immunogenicity would not be decreased. Again, Applicant submits that this is not ambiguous.

I. The Examiner rejects Claim 24 as being indefinite for use of the expression "sequences that bind to T cell epitope." New claim 33 recites "decreased T cell immunogenicity as compared to said target protein", and thus the standard of reference is present.

It is respectfully submitted that Applicant has overcome the rejections under 35 USC § 112, second paragraph by the above amendments and discussion.

Rejection – 35 USC § 112, first paragraph

The Examiner has rejected Claims 24 and 32 under 35 USC § 112, first paragraph. It is assumed that Claim 32 is rejected for being dependent upon Claim 24.

3. The Examiner rejects Claims 24 and 32 for containing the term "selecting". Without admitting the propriety of the rejection, and to further the prosecution, the term has been altered to "identifying", as outlined in the original claims. The specification states "at least one candidate variant protein is identified in which at least one sequence capable of interacting with . . . a TCR . . . has been altered" (see page 38, lines 31-33) and goes on to describe possible immunogenicity screening/selection methods on page 39, lines 6-12. Similarly, page 61, lines 20-29 outline methods for testing for altered immunogenicity, references a number of specific methods for identifying altered T cell immunogenicity.

With respect to the Examiner's statement that "there is no disclosure of synthesizing of various proteins having more than one immunogenic sequence", the specification clearly outlines the generation of proteins with more than one altered immunogenic sequence (see page 31, line 7; see page 37, lines 28 to 36, among others).

4. Claims 24 and 32 are rejected based on the use of the expression "sequences that bind to T cell epitopes" as new matter and that there is no guidance on how to practice the claimed method with such method step. New claim 33 obviates the rejection.

5. Claim 24 and 32 were rejected on the basis that the specification does not enable the creation of variant proteins with altered immunogenicity. As a preliminary matter, the

Examiner has previously stated that any protein with a "different amino acid content will inevitably have altered immunogenicity" (see page 4). This appears inconsistent with the present rejection.

In any event, the Examiner agrees that the Applicant was in possession of method of determining binding to MHC molecules, referencing papers that are not 100% accurate (Applicant notes that 100% accuracy has never been a requirement of patentability; see In re Angstadt, 190 USPQ 214, 218 (CCPA 1976).

Also, not all methods for identifying MHC-binding peptides are so poorly predictive; for example, methods that rely on experimental, in vitro MHC binding are, by definition, capable of accurately determining whether a peptide is capable of binding an MHC (i.e., accuracy will approach 100%; these methods are referenced in Sidney, J., et al. and Hammer et al., and are included in the specification). In addition, predictive methods including artificial neural networks (e.g., Brusic et al.) and virtual matrix approaches (e.g., Sturniolo et al.) are far more accurate than 33%. Altering the sequence of a MHC-binding peptide so that it is no longer capable of MHC binding will alter the peptide's ability to trigger an immune response since no antigen will be presented to T cells and will therefore, by definition, decrease its immunogenicity relative to the original peptide sequence.

New claim 33 recites "decreased immunogenicity". Decreasing binding of a peptide sequence to a TCR and/or preventing the formation of a TCR-peptide-MHC complex (e.g., by decreasing peptide binding to a MHC) will decrease immunogenicity. The protein design methods outlined in the present invention allow the identification of proteins with decreased immunogenicity.

7. Claims 24 and 32 are rejected as not being enabled for failure in the specification to provide an example.

Applicants respectfully point out that a working example is not required, and that given the sheer volume of identified T cell antigens and the knowledge in the art, using in silico methods to decrease immunogenicity are enabled.

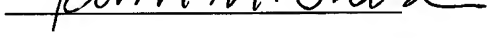
Reconsideration of the claims, as amended, is respectfully requested.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Dated: October 13, 2004

By: 

4 Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Fax No. (415) 398-3249

Robin M. Silva, Reg. No. 38,304

Filed under 37 C.F.R. § 1.34(a)

Customer No. 32940